REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claims 1 and 12 have been amended to recite that the recombinant multimeric protein (Claim 1) or the heterologous nucleic acid sequence which encodes a protein (Claim 12)

Claims 27 to 31 have been added. Support for "activates complement to induce opsonization of cells" appears at least on page 9, lines 30 to 35 of the specification. Support for "a ligand of the immune system" in Claims 29 and 30 appears at least on page 6, lines 7 to 10 of the specification. Support for activates, modulates or inhibits complement appears at least on page 9, lines 22-23 of the specification. Applicants submit that no new matter has been added via this claim amendment.

Turning now to the Official Action, Claims 1, 4 to 12, 17, 20, 23 and 26 have been rejected under 35 U.S.C. § 102(b) as being anticipated by WO 91/11461. For the following reasons, this rejection is respectfully traversed.

In maintaining this rejection, the Examiner purports that since the β chain of C4BP is disclosed by reference at page 4, lines 12 to 17 of WO 91/11461 and since the β chain of C4BP was cloned at the time of the present invention as evidenced by Hillarp et al, PNAS, Vol. 87 (3) pp. 1183-1187 (1990) the presently claimed invention is anticipated by WO 91/11461. However, the mere fact that the β chain of C4BP was known, does not mean that it was included in the C4BP fusion protein described in WO91/11461 either extrinsically or intrinsically, as will be clearly demonstrated below.

First of all, the Examiner relies on the publication of Hillarp and Dahlback, *The Journal of Biochemistry*, **Vol** 263, No. 25 pp. 12759-12764 (1988) which is solely cited

in the Background of the Invention of WO91/11461 and is not referred to in the Summary of the Invention, the Description of the Preferred Embodiments or in the Examples. Hence, this publication is not technically relied upon for the C4BP construct, but is merely background information.

Furthermore, this JBC publication describes a new 45 kDa subunit in C4BP. However, what the skilled artisan learns from the teachings of Hillarp and Dahlback (JBC) is that the amino acid sequence of this 45 kDa protein is different from that of the 70 kDa protein. More specifically, the authors state the following:

> The data were sufficient to demonstrate that the sequence of the 45-kDA peptide is distinct from that of the 70-kDa subunit and that the 45-kDa peptide is not derived from the 70-kDA subunit. A data search against amino acid sequences in the NBRF databank revealed no identity with any other sequence present in the databank.

This difference is important, especially in view of the disclosure in WO91/11461. Furthermore, there is no mention in this reference that this 45-kDa protein is a β chain of C4BP.

The other reference referred to by the Examiner in the Official Action is Hillarp et al (PNAS). This reference discloses the isolation and cloning of the β-chain of C4BP, which is a 45-kDa protein, referred to previously in the Hillarp et al JBC paper. The nucleotide sequence and derived amino acid sequence is depicted in Figure 2. There are 235 amino acids for this β-chain. Reference is also made to the α-chain of C4BP and it is known that this alpha chain is composed of 549 amino acids.

More specifically at page 1183 of Hillarp et al (PNAS) the following is stated with respect to the α chain of C4BP:

> The α chain is composed of **549 amino acid residues** and the 491 N-terminal residues can be divided into eight short consensus repeats (SCRs) (emphasis added).

With respect to the β-chain of C4BP, Hillarp et al (PNAS) state the following:

> As deduced from its cDNA sequence the mature β chain consists of **235 amino acid residues** (emphasis added).

Therefore the entire α and β chains of C4BP would have a total length of 784 amino acids or 2,352 nucleotides.

WO91/11461 discloses C4 binding protein fusion proteins. It is stated at page 9 of the specification that "C4 binding protein" ("C4BP") refers to a polypeptide sequence depicted in Figure 1 from amino acids -32 to +549.

It is also stated at page 7 under the description of the drawings that Figures 1A to 1C depict the DNA sequence and deduced amino acid sequence of human C4BP polypeptide derived from pJOD.C4BP.3. Furthermore, it is stated that:

> Throughout this application, references to C4BP by amino acid formula correspond to the coordinate system set forth in this figure (i.e., Figure 1).

The amino acid sequence in Figure 1 has 549 amino acids. This amino acid sequence is not that of the β chain as can be seen from the comparison of this sequence with those described in Hillarp et al, (PNAS) *supra*.

More specifically, the sequence in Figure 1 of WO91/11461 starts with Met Ala Ala Trp Pro and ends with Asp Lys Glu Leu, while the sequence for the β chain of C4BP described in Figure 2 of Hillarp et al starts with Met Phe Phe Trp Cys and ends with Ala Lys Leu Leu. Thus, there is no sequence of the β chain of C4BP in WO91/11461, as can be concluded by the comparison of Figure 1, which is the α chain with the β chain set forth in Hillarp (PNAS).

Furthermore, when reviewing the Examples of WO91/11461, it is clear that a full length and smaller constructs of the α chain of C4BP were used to create the fusion proteins. Thus, at page 32 in Example I, the following was stated:

This produced a 1746 bp fragment encoding C4BP and bordered by transcriptional start and stop signals. We verified the identity of this fragment by digestion with SnaBI and with PstI. As predicted by the DNA sequence of C4BP, SnaBI digestion produced a 1436 bp fragment and SnaBI/PstI digestion produced a 1047 bp fragment.
Then we inserted the C4BP-encoding fragment into the animal expression vector, pJOD-S, which was created as follows(See Figures 6B-6C).

Another set of constructs is set forth in Example IV of WO91/11461, where a 1648 by fragment of C4BP encoding SCR8-SCR1 and the C4BP core was performed using PCR with pJOD.C4BP.3 linearized with *Not*I. The C4BP core is further defined at page 10 of this document as encompassing "at a minimum amino acids +498 to +549 of Figure 1 and, preferably amino acids +492 to +549."

Further constructs of 1089 bp fragments of C4BP, 908 bp fragment of C4BP, 711 bp fragment of C4BP and 353 bp fragment of C4BP were also produced in Example IV. Thus, the total number of nucleotides in these constructs was 1648, which is a total of 549 amino acids. This is the α chain of C4BP, since it is clear from the cited references by the Examiner, as well as a comparison of the sequences that the β chain was not used.

Furthermore, with respect to the fact that the Examiner relies on the teachings in WO91/11461 that monomeric C4BP fusion proteins were produced, Applicants refer the Examiner to at least page 10 of the specification, in which the definition of the C4BP monomer is defined; i.e., it comprises a C4BP core or at least one SCR fused to the N-terminus of the C4BP core. Thus the "C4BP core: encompasses, a defined above amino acids +498 to +549 in Figure 1, while the SCR loops encompass "amino acids +2 to +6- of SCR8, +65 to +122 of SCR7, +127 to +186 of SCR6, +191 to +246 of SCR5, +251 to +312 of SCR4, +316 to +375 of SCR3, +378 to +432 of SCR2 and +446 to +490 of SCR1." In other words the C4BP part of the fusion protein does not exceed 549 amino acids and thus cannot contain the β chain since it has a totally different amino acid sequence, as demonstrated by the above comparison.

Since none of the preferred embodiments nor examples rely or use on the β chain of C4BP in WO91/11461 as demonstrated above, it can be concluded that this reference does not anticipate the presently claimed invention.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. § 102(b) as being anticipated by WO 91/11461. For the following reasons, this rejection is respectfully traversed.

These claims are directed to host cells and methods for preparing a multimeric protein using recombinant host cells and recite a heterologous nucleic acid sequence which encodes at least one polypeptide fusion molecule B which consists of a cysteine-containing C-terminal fragment of the β chain of C4BP.

As set forth above and explained in greater detail, WO91/11461 does not disclose such a fusion protein having the β chain of C4BP. Those arguments set forth above in the other novelty rejection are therefore incorporated herein for the present rejection.

Therefore, the presently claimed invention is not anticipated by this reference.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 2, 3, 13 to 16, 22, 24 and 25 remain objected to. Applicants request that this rejection be held in abeyance until there is clearly allowed subject matter.

Claims 1 to 17, 20, 22 to 26 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. For the following reasons, this rejection is respectfully traversed.

In rendering this rejection the Examiner maintains that the claimed molecules "may not be operable within the framework of the present invention" and thus concludes that the specific claims cited in this rejection lack enablement.

First of all, Applicants submit that it is not the function of the claims to specifically exclude possible inoperative embodiments. See, *In re Dinh-Nguyen*, 492 F. 2d 856, 181 USPQ 46, 48 (CCPA 1974).

Thus, the Examiner's conclusion that some of the claimed fragments, heterologous molecules and CD lymphocyte surface proteins may not be operable and thus these claims are too broad and lack enablement has no basis in the law and cannot be maintained.

Secondly, the PTO Board of Appeal has recognized that inoperative embodiments in a claim would be recognized by the skilled artisan and that the skilled artisan would find no benefit in seeking out embodiments that do not work. This is clear from the teachings of *Ex parte Cole*, 223 USPQ 94, 95-96 (PTO Bd. App. 1983) wherein the Board stated the following:

> Claims are addressed to the person of average skill in the particular art. Compliance with 112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination.

Moreover, even if inoperative embodiments are encompassed by the claims, the knowledge of the skilled artisan must be taken into consideration in deciding whether an

enablement rejection is appropriate. This fact is illustrated in *In re Cook,* 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971) as set forth in the following quotation:

> ....many patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit factors which must be presumed to be within the level of ordinary skill in the art...There is nothing wrong with this so long as it would be obvious to one of ordinary skilled in the relevant art how to include those factors in such manner to make the embodiment operative rather than inoperative.

Applicants respectfully submit that the skilled artisan could easily attain factors which make the embodiment operative. Because of the high level of skill in this art, **less is required** to teach people how to make and use the invention and less is required to make an inoperative embodiment an operative one. This is due to the fact that a Patent Applicant need not restate that which is already known in the art.

It should be recalled at this point that the ultimate question in an enablement issue is whether or not the specification contains a sufficiently explicit disclosure to enable one skilled in the art to produce the invention without the exercise of undue experimentation. As stated in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int 1986):

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention.

Applicants submit that in view of the high level of skill and the knowledge of the art at the time this invention was filed that it would not be undue experimentation for the skilled artisan to select various and appropriate fragments and heterolgous molecules and CD lymphocyte surface proteins and use them in the claimed construct according to their desired application.

Indeed, one of the purposes of the present invention is to provide a recombinant multimeric protein comprising a polypeptide fusion monomer A of the C-terminal

fragment of the α chain of C4BP linked to a polypeptide fusion monomer fragment of the β chain of C4BP. Each of these fusion monomers contain a heterologous polypeptide fragment which can be altered according to the desired application. This is evidenced at least on pages 3 and 6 of the application and a person skilled in this art would adapt the recombinant multimeric protein according to its particular uses. Thus to limit these particular heterologous fragments to particular specific examples would be unduly burdensome and would not reflect the present invention.

In summary, Applicants submit that the presently claimed invention can be practiced without undue experimentation and although the claims may encompass inoperative embodiments 35 U.S.C. § 112, first paragraph does not require that the claims encompass only operative embodiments.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 1 to 17, 20 and 22 to 26 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. For the following reasons, this rejection is respectfully traversed.

Applicants submit that the present specification does in fact convey with reasonable clarity to the person skilled in the art that the inventors had in fact possession of the claimed invention. As stated by the court in *ADCO Products, Inc. v, Carlisle Syntec Inc.*, 110 F. Supp. 2d 276, 291 (D.Del. 2000):

> It is not necessary for an applicant to describe exactly the subject matter claimed, so long as the written description allows the person of **ordinary skill in the art to recognize that the applicant invented what is claimed** (emphasis added).

Applicants submit that when a skilled artisan peruses the specification, it is clear what types of heterologous molecules, fragments, therapeutic enzymes and antigens can be used in the recombinant multimeric proteins, since each heterologous molecule, fragments, therapeutic enzymes and antigens are chosen for their particular application.

The particular applications are in fact set forth in the application. For instance, at least page 3, which discloses that the recombinant multimeric proteins are used to achieve immunointervention in human immune pathologies. These interventions can relate to the pathology of transport and elimination of immune complexes by erythrocytes in such illnesses as disseminated lupus erythematosus and HIV infections; capturing antigens which are mediated by Fc receptors on cell surfaces of monocyte/macrophage cell lines; modulation of molecules having soluble CD16 activity; prevention of anti-erythrocyte Rh(D) alloimmunization; and the inhibition of cell penetration of HIV using soluble forms of CD4, antibodies directed against HIV and/or molecules with enzymatic function.

Furthermore, at page 9 of the specification more specific applications are cited such as the prevention of fetomaternal alloimmunization, therapy or prophylaxis of viral, bacterial or parasitic infections and therapy of autoimmune diseases such as disseminated lupus erythematosus, alloimmune disease or that the recombinant multimeric protein activates, modulates or inhibits complement.

In fact, page 9 of the specification explains to the skilled artisan in a general manner what the present invention can be used for as stated below:

> More generally, the present invention relates to the use of a recombinant protein as previously defined in the production of a medicament which makes it possible, depending on the functionality which is attributed to the to the ligands or the receptors, to effect an immunointervention, in particular in the opsonization or non-opsonization of target cells by means of activating, modulating or inhibiting complement.

Thus, the skilled artisan would know which particular heterologous polypeptides, fragments, enzymes, antigens to choose from based on the chosen application. There are not an unlimited number of heterologous polypeptides, fragments, enzymes, antigens to choose from, since the choice requires that immunointervention be achieved.

Moreover, at least page 6 of the specification describes certain species that can be used such as fragments from lymphocyte proteins such as CD4, CD8, CD16 and CD35 (or CR1); antibodies of fragments thereof having anti-erythrocyte specificity and in particular anti-Rh(D) specificity; vaccinating antigens and therapeutic enzymes.

Therefore the teaching in the specification of particular applications and what the present invention needs to achieve, as well as specific examples of various species of the heterologous polypeptide fragments, coupled with the high level of skill in this art, it can only be concluded that the inventors do in fact have possession of the claimed invention.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Please charge our Deposit Account No. 22-0261 in the amount of $1,000.00 covering the fee set forth in 37 CFR 1.16(f). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 22-0261, under Order No. 31640-134353.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Respectfully submitted,

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